Docket No.: PF-0802 US

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By: _____ Printed: Lisa McDill.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Lal et al.

Title:	CYTOCHROME P450 VARIANT		
Serial No.:	09/905,370	Filing Date:	July 12, 2001
Examiner:	Slobodyansky, E.	Group Art Unit:	1652

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Commissioner for Patents
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DECLARATION OF DR. TOD BEDILION
UNDER 37 C.F.R. § 1.132

I, TOD BEDILION, a citizen of the United States, residing at 132 Winding Way, San Carlos, California, declare that:

1. I was employed by Incyte Genomics, Inc. (now known as Incyte Corporation; hereinafter "Incyte") as a Director of Corporate Development until May 11, 2001. I am currently under contract to be a Consultant to Incyte.

2. In 1996, I received a Ph.D. degree in Cell, Molecular and Development Biology from UCLA. I had previously received, in 1988, a B.S. degree in biology from UCLA.

Upon my graduation from UCLA, I became, in April 1996, the first employee of Synteni, Inc. (hereinafter "Synteni"). I was a Research Director at Synteni from April 1996 until Synteni was acquired by Incyte in early 1998.

I understand that Synteni was founded in 1994 by T. Dari Shalon while he was a graduate student at Stanford University. I further understand that Synteni was founded for the purpose of commercially exploiting certain "cDNA microarray" technology that was being worked on at Stanford in the early to mid-1990s. That technology, which I will sometimes refer to herein as the "Stanford-developed cDNA microarray technology", was the subject of Dr. Shalon's doctoral thesis at Stanford. I understand and believe that Dr. P.O. Brown was Dr. Shalon's thesis advisor at Stanford.

During the period beginning before I was employed by Synteni and ending upon its acquisition by Incyte in early 1998, I understand Synteni was the exclusive licensee of the Stanford-developed cDNA microarray technology, subject to any right that the United States government may have with respect to that technology. In early 1998, I understand Incyte acquired rights under the Stanford-developed cDNA microarray technology as part of its acquisition of Synteni.

I understand that at the time of the commencement of my employment at Synteni in April 1996, Synteni's rights with respect to the Stanford-developed cDNA technology included rights under a United States patent application that had been filed June 7, 1995 in the names of Drs. Brown and Shalon and that subsequently issued as United States Patent No. 5,807,522 (the Brown '522 patent). In December 1995, the subject matter of the Brown '522 patent was published based on a PCT patent application that had also been filed in June 1995. The Brown '522 patent (and its corresponding PCT application) describes the use of the Stanford-developed cDNA technology in a number of gene expression monitoring applications, as will be discussed more fully below.

Upon Incyte's acquisition of Synteni, I became employed by Incyte. From early 1998 until late 1999, I was an Associate Research Director at Incyte. In late 1999, I was promoted to the position of Director, Corporate Development.

I have been aware of the Stanford-developed cDNA microarray technology since shortly before I commenced my employment at Synteni. While I was employed by Synteni, virtually all (if not all) of my work efforts (as well as the work efforts of others employed by Synteni) were directed to the further development and commercial exploitation of that cDNA microarray technology. By the end of 1997, those efforts had progressed to the point that I understand Incyte agreed to pay at least about $80 million to acquire Synteni. While I was employed by

Incyte, I continued to work on the further development and commercial exploitation of the cDNA microarray technology that was first developed at Stanford in the early to mid-1990s.

3. I have reviewed the specification of a United States patent application that I understand was filed on July 12, 2001 in the names of Preeti Lal et al. and was assigned Serial No. 09/905,370 (hereinafter "the Lal '370 application"). Furthermore, I understand that this United States patent application claims the benefit of United States provisional patent application Serial No. 60/218,934, filed on July 14, 2000 (hereinafter "the Lal '934 application"). The Lal '370 and Lal '934 applications were filed with essentially identical specifications, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the Lal '370 and Lal '934 applications. My remarks herein will therefore be directed to the Lal '934 patent application, and July 14, 2000, as the relevant date of filing. In broad overview, the Lal '934 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene expression monitoring applications that are useful in connection with (a) developing drugs (e.g., the diagnosis of inherited and acquired genetic disorders, expression profiling, toxicology testing, and drug development with respect to cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Lal '370 application contains claims that are directed to isolated polynucleotides having the sequences of SEQ ID NO:1-encoding polynucleotides, for example SEQ ID NO:2 (hereinafter "the SEQ ID NO:1-encoding polynucleotides"), and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Lal '370 application does not disclose a credible, specific and substantial asserted utility or a well established utility for the claimed SEQ ID NO:1-encoding polynucleotides. I further understand that whether or not a patent specification discloses a credible, specific and substantial asserted utility or a well established utility for its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time the patent application was filed. In addition, I understand that a credible, specific and substantial asserted utility or a well established utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Lal '370 application and its parent, the Lal '934 application, do not disclose a credible, specific and substantial asserted "real-world" utility for the SEQ ID NO:1-encoding polynucleotides, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Lal '934 application pertains on July 14, 2000, would have concluded that the Lal '934 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:1-encoding polynucleotides in their then available and disclosed forms. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107.01 of the Manual of Patent Examining Procedure, under the heading "I. 'Real-World Value' Requirement":

> "Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm."

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Lal '934 patent application disclosed to a person skilled in the art at the time of its filing a number of credible, specific and substantial real-world utilities for the claimed SEQ ID NO:1-encoding polynucleotides. More specifically, persons skilled in the art on July 14, 2000 would have understood the Lal '934 application to disclose the use of the SEQ ID NO:1-encoding polynucleotides in a number of gene expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-16 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Lal '934 application, and (b) a number of published articles and patent documents that evidence gene expression monitoring techniques that were well-known before the July 14, 2000 filing date of the Lal '934 application. The published articles and patent documents I considered are:

(a) Schena, M., Shalon, D., Heller, R., Chai, A., Brown, P.O., Davis, R.W., Parallel Human Genome Analysis: Microarray-based Expression Monitoring of 1000 Genes, Proceedings of the National Academy of Sciences USA, 93, 10614-10619 (1996) (hereinafter "the Schena 1996 article") (copy annexed at Tab A);

(b) Schena, M., Shalon, D., Davis, R.W., Brown, P.O., Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray, Science, 270, 467-470 (1995) (hereinafter "the Schena 1995 article") (copy annexed at Tab B);

(c) Shalon and Brown PCT patent application WO 95/35505 entitled "Method and Apparatus For Fabricating Microarrays Of Biological Samples," filed on June 16, 1995, and published on December 28, 1995 (hereinafter "the Shalon PCT application") (copy annexed at Tab C);

(d) Brown and Shalon U.S. Patent No. 5,807,522, corresponding to the Shalon PCT application, entitled "Methods For Fabricating Microarrays Of Biological Samples," filed on June 7, 1995 and issued on September 15, 1998 (hereinafter "the Brown '522 patent") (copy annexed at Tab D);

(e) DeRisi, J., Penland, L., Brown, P.O. (Group 1); Bittner, M.L., Meltzer, P.S., Ray, M., Chen, Y., Su, Y.A., Trent, J.M. (Group 2), Use of a cDNA Microarray to Analyse Gene Expression Patterns in Human Cancer, Nature Genetics, 14(4), 457-460 (1996) (hereinafter "the DeRisi article") (copy annexed at Tab E);

(f) Shalon, D., Smith, S.J., Brown, P.O., A DNA Microarray System for Analyzing Complex DNA Samples Using Two-color Fluorescent Probe Hybridization, Genome Research, 6(7), 639-645 (1996) (hereinafter "the Shalon article") (copy annexed at Tab F);

(g) Heller, R.A., Schena, M., Chai A., Shalon, D., Bedilion, T., Gilmore, J., Woolley, D.E., Davis R.W., Discovery and Analysis of Inflammatory Disease-related Genes Using cDNA Microarrays, Proceedings of the National Academy of Sciences USA, 94, 2150-2155 (1997) (hereinafter "the Heller article") (copy annexed at Tab G); and

(h) Sambrook, J., Fritsch, E.F., Maniatis, T., Molecular Cloning, A Laboratory Manual, pages 7.37 and 7.38, Cold Spring Harbor Press (1989) (hereinafter "the Sambrook Manual") (copy annexed at Tab H).

8. Many of the published articles and patent documents I considered (i.e., at least items (a)-(g) identified in paragraph 7) relate to work done at Stanford University in the early and mid-1990s with respect to the development of cDNA microarrays for use in gene expression monitoring applications, under which Synteni became exclusively licensed. As I will discuss below, a person skilled in the art who read the Lal '934 application on July 14, 2000 would have understood that application to disclose the SEQ ID NO:1-encoding polynucleotides to be useful for a number of gene expression monitoring applications, e.g., as probes for the expression of those specific polynucleotides in cDNA microarrays of the type first developed at Stanford.

Furthermore, items (a)-(g) establish that monitoring the expression of genes using microarrays was a well-known and established method routinely used in toxicology testing and drug development at the time of filing of the Lal '934 application and for several years prior to July 14, 2000. As such, one of ordinary skill in the art would have recognized that the SEQ ID NO:1-encoding polynucleotides could be used in toxicology testing and drug development, irrespective of the biological functions of their encoded polypeptide.

9. Turning more specifically to the Lal '934 specification, the SEQ ID NO:2 polynucleotide is shown as one of two sequences under the heading "Sequence Listing." The Lal '934 specification specifically teaches that the invention provides an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:1 (Lal '934 application at, e.g., page 3, lines 14-16). In an alternative of the invention, the polynucleotide has the sequence of SEQ ID NO:2 (Lal '934 application at, e.g., page 3, lines 20-22). The specification further teaches that (a) the SEQ ID NO:2 polynucleotide includes cDNA sequences obtained from a human liver tumor cDNA library, (b) the SEQ ID NO:2 polynucleotide encodes the cytochrome P450 variant shown as SEQ ID NO:1 and referred to as "CYTPV" or "CYTPV-1," and (c) "the expression of CYTPV is closely associated with liver tumor tissue" and therefore "CYTPV appears to play a role in cell proliferative, developmental, autoimmune/inflammatory,

liver and metabolic disorders" (Lal '934 application at page 3, lines 5-6 and 20-22; page 21, lines 21-24; page 34, lines 20-22; and Tables 4, 5, and 6).

The Lal '934 application discusses a number of uses of the SEQ ID NO:1-encoding polynucleotides in addition to their use in gene expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding whether or not the Lal '934 specification discloses these additional uses to be substantial, specific and credible real-world utilities of the SEQ ID NO:1-encoding polynucleotides. Consequently, my discussion in this Declaration concerning the Lal '934 application focuses on the portions of the application that relate to the use of the SEQ ID NO:1-encoding polynucleotides in gene expression monitoring applications.

10. The Lal '934 application discloses that the polynucleotide sequences disclosed therein, including the SEQ ID NO:1-encoding polynucleotides, are useful as probes in microarrays. It further teaches that the microarrays can be used to "monitor the relative expression levels of large numbers of genes simutaneously" for a number of purposes, including "to develop and monitor the activities of therapeutic agents" (Lal '934 application at page 51, lines 9-20). Microarrays can also be used for "toxicological testing of industrial and naturally-occurring environmental compounds" (Lal '934 application at page 52, lines 4-7) and for assessing "the toxicity of a test compound" (Lal '934 application at page 52, lines 24-25).

The Lal '934 application teaches that microarrays can be prepared using the previously mentioned cDNA microarray technology developed at Stanford in the early to mid-1990s. In this connection, the Lal '934 application specifically cites to the Schena 1996 article identified in item (a) of paragraph 7 of this Declaration (Lal '934 application at page 52, lines 31-35; see paragraph 7, *supra*).

The Schena 1996 article is one of a number of documents that were published prior to the July 14, 2000 filing date of the Lal '934 application that describes the use of the Stanford-developed cDNA microarray technology in a wide range of gene expression monitoring applications, including monitoring and analyzing gene expression patterns in human cancer. In view of the Lal '934 application, the Schena 1996 article, and other related pre-July 2000 publications, persons skilled in the art on July 14, 2000 clearly would have understood the Lal '934 application to disclose the SEQ ID NO:1-encoding polynucleotides to be useful in cDNA

microarrays for the development of new drugs and for monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 15 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development in July 2000 (and for many years prior to July 2000) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identifying undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. The Lal '934 application discloses the use of the SEQ ID NO:1-encoding polynucleotides in toxicity studies for the development and the monitoring of the activities of drugs, including by differential gene expression analysis (Lal '934 application at page 52, lines 4-30), and persons skilled in the art who read the Lal '934 application on July 14, 2000 would have understood that to be so.

11. The Schena 1996 article was not the first publication that described the use of the cDNA microarray technique developed at Stanford to monitor quantitatively gene expression patterns. More than a year earlier (ie., in October 1995), the Schena 1995 article, entitled "Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray," was published (see Tabs A and B).

12. As previously discussed (paragraphs 2 and 7, *supra*), in the mid-1990s patent applications were filed in the names of Drs. Shalon and Brown that described the Stanford-developed cDNA microarray technology. The two patent documents (i.e., the Shalon PCT application and the Brown '522 patent) annexed to this Declaration at Tabs C and D evidence

information that was available to the public regarding the Stanford-developed cDNA microarray technology before the July 14, 2000 filing date of the Lal '934 application.

The Shalon PCT patent application, which was published in December 1995, contains virtually the same (if not exactly the same) specification as the Brown '522 patent. Hence, the Brown '522 patent disclosure was, in effect, available to the public as of the December 1995 publication date of the Shalon PCT application (see Tabs C and D). For the sake of convenience, I cite to and discuss the Brown '522 specification below on the understanding that the descriptions in that specification were published as of the December 28, 1995 publication date of the Shalon PCT application.

The Brown '522 patent discusses, in detail, the utility of the Stanford-developed cDNA microarrays in gene expression monitoring applications. For example, in the "Summary Of The Invention" section, the Brown '522 patent teaches (see Tab D, col. 4, line 52-col. 5, line 8):

> Also forming part of the invention is a method of detecting differential expression of each of a plurality of genes in a first cell type, with respect to expression of the same genes in a second cell type. In practicing the method, there is first produced fluorescent-labeled cDNAs from mRNAs isolated from two cells types, where the cDNAs from the first and second cell types are labeled with first and second different flourescent reporters.
>
> A mixture of the labeled cDNAs from the two cell types is added to an array of polynucleotides representing a plurality of known genes derived from the two cell types, under conditions that result in hybridization of the cDNAs to complementary-sequence polynucleotides in the array. The array is then examined by fluorescence under fluorescence excitation conditions in which (i) polynucleotides in the array that are hybridized predominantly to cDNAs derived from one of the first or second cell types give a distinct first and second fluorescence emission color, respectively, and (ii) polynucleotides in the array that are hybridized to substantially equal numbers of cDNAs derived from the first and second cell types give a distinct combined fluorescence emission color, respectively. The relative expression of known genes in the two cell types can then be determined by the observed fluorescence emission color of each spot.

The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays

disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58; and col. 18, lines 25-30).

13. Also pertinent to my considerations underlying this Declaration is the DeRisi article, published in December 1996. The DeRisi article describes the use of the Stanford-developed cDNA microarray technology "to analyze gene expression patterns in human cancer" (see Tab E at, e.g., page 457). The DeRisi article specifically indicates, consistent with what was apparent to persons skilled in the art in July 2000, that increasing the number of genes on the cDNA microarray permits a "more comprehensive survey of gene expression patterns," thereby enhancing the ability of the cDNA microarray to provide "new and useful insights into human biology and a deeper understanding of the gene pathways involved in the pathogenesis of cancer and other diseases" (see Tab E at page 458).

14. Other pre-July 2000 publications further evidence the utility of the cDNA microarrays first developed at Stanford in a wide range of gene expression monitoring applications (see, e.g., the Shalon and the Heller articles at Tabs F and G). By no later than the March 1997 publication of the Heller article, these publications showed that employees of Synteni (i.e., James Gilmore and myself) had used the cDNA microarrays in specific gene expression monitoring applications (see Tab G).

The Heller article states that the results reported therein "successfully demonstrate the use of the cDNA microarray system as a general approach for dissecting human diseases" (Tab G at page 2150). Among other things, the Heller article describes the investigation of "1000 human genes that were randomly selected from a peripheral human blood cell library" and "[t]heir differential and quantitative expression analysis in cells of the joint tissue. . . to demonstrate the utility of the microarray method to analyze complex diseases by their pattern of gene expression" (see Tab G at pp. 2150 *et seq.*).

Much of the work reported on in the Heller article was done in 1996. That article, therefore, evidences how persons skilled in the art were readily able, well prior to July 2000, to make and use cDNA microarrays to achieve highly useful results. For example, as reported in the Heller article, a cDNA microarray that was used in some of the highly successful work

reported on therein was made from 1,000 genes randomly selected from a human blood cell library.

15. A person skilled in the art on July 14, 2000, who read the Lal '934 application, would understand that application to disclose the SEQ ID NO:1-encoding polynucleotides (for example, SEQ ID NO:2) to be highly useful as probes for the expression of those specific polynucleotides in cDNA microarrays of the type first developed at Stanford. For example, the specification of the Lal '934 application would have led a person skilled in the art on July 14, 2000, who was using gene expression monitoring in connection with developing new drugs for the treatment of cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders, to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1-encoding polynucleotides. Persons skilled in the art would appreciate that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders, for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(f) below a number of reasons why a person skilled in the art, who read the Lal '934 specification on July 14, 2000, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:1-encoding polynucleotides would be highly useful tools for inclusion in cDNA microarrays for evaluating the efficacy and toxicity of proposed drugs for cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders, as well as for other evaluations:

(a) The Lal '934 application teaches the SEQ ID NO:1-encoding polynucleotides to be useful as probes in cDNA microarrays of the type first developed at Stanford. It also teaches that such cDNA microarrays are useful in a number of gene expression monitoring applications, including in developing and monitoring the activity of therapeutic agents [i.e., drugs] (see paragraph 10, *supra*).

(b) By July 2000, the Stanford-developed cDNA microarray technology was a well known and widely accepted tool for use in a wide range of gene expression monitoring applications. This is evidenced, for example, by numerous publications describing the use of that cDNA technology in gene expression monitoring applications and the fact that, for over a year, the technology had provided the basis for the operations of an up-and-running company (Synteni), with employees, that was created for the purpose of developing and commercially exploiting that technology (see paragraphs 2, 8, and 10-14, *supra*). The fact that Incyte agreed to purchase Synteni in late 1997 for an amount reported to be at least about $80 million only serves to underscore the substantial practical and commercial significance, in 1997, of the cDNA microarray technology first developed at Stanford (see paragraph 2, *supra*).

(c) The pre-July 2000 publications regarding the cDNA microarray technology first developed at Stanford that I discuss in this Declaration repeatedly confirm that, consistent with the teachings in the Lal '934 application, cDNA microarrays are highly useful tools for conducting gene expression monitoring applications with respect to the development of drugs and the monitoring of their activity. Among other things, those pre-July 2000 publications confirmed that cDNA microarrays (i) were useful for monitoring gene expression responses to different drugs (see paragraph 12, *supra*), (ii) were useful in analyzing gene expression patterns in human cancer, with increasing the number of genes on the cDNA microarray enhancing the ability of the cDNA microarray to provide useful information (see paragraph 13, *supra*), and (iii) were a valuable tool for use as part of a "general approach for dissecting human diseases" and for "analyz[ing] complex diseases by their pattern of gene expression" (see paragraph 14, *supra*).

(d) Based on my own extensive work for a company whose business was the development and commercial exploitation of cDNA microarray technology for more than two years prior to the July 2000 filing date of the Lal '934 application, I have first-hand knowledge concerning the state of the art with respect to making and using cDNA microarrays as of July 14, 2000 (see paragraphs 2 and 14, *supra*). Persons skilled in the art as of that date would have (i) concluded that the Lal '934 application disclosed cDNA microarrays containing the SEQ ID NO:1-encoding polynucleotides to be useful, and (ii) readily been able to make and use such microarrays with useful results.

(e) The Lal '934 specification contains a number of teachings that would lead persons skilled in the art on July 14, 2000 to conclude that a cDNA microarray that contained the

SEQ ID NO:1-encoding polynucleotides would be a more useful tool for gene expression monitoring applications relating to drugs for treating cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders than a cDNA microarray that did not contain the SEQ ID NO:1-encoding polynucleotides. Among other things, the Lal '934 specification teaches that (i) the SEQ ID NO:2 polynucleotide includes cDNA sequences obtained from a human liver tumor cDNA library, (ii) the SEQ ID NO:2 polynucleotide encodes the cytochrome P450 variant shown as SEQ ID NO:1 and referred to as "CYTPV" or "CYTPV-1," and (iii) "the expression of CYTPV is closely associated with liver tumor tissue" and therefore "CYTPV appears to play a role in cell proliferative, developmental, autoimmune/inflammatory, liver and metabolic disorders" (Lal '934 application at page 3, lines 5-6 and 20-22; page 21, lines 21-24; page 34, lines 20-22; and Tables 4, 5, and 6; see paragraph 9, *supra*).

(f) Persons skilled in the art on July 14, 2000 would have appreciated (i) that the gene expression monitoring results obtained using a cDNA microarray containing a probe to a sequence selected from the group consisting of SEQ ID NO:1-encoding polynucleotides would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the probe to a SEQ ID NO:1-encoding polynucleotide, and from the cDNA microarray as a whole (including all its other individual probes). These kinds of varying results, depending on the identity of the drug being tested, in no way detract from my conclusion that persons skilled in the art on July 14, 2000, having read the Lal '934 specification, would specifically request that any cDNA microarray that was being used for conducting gene expression monitoring studies on drugs for treating cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) contain a probe to a SEQ ID NO:1-encoding polynucleotide. Persons skilled in the art on July 14, 2000 would have wanted their cDNA microarray to have a probe to a SEQ ID NO:1-encoding polynucleotide because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to July 14, 2000.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 15, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Lal '934 application disclosing to persons skilled in the art at the time of its filing credible, specific and substantial real-world utilities for the SEQ ID NO:1-encoding polynucleotides.

16. Also pertinent to my considerations underlying this Declaration is the fact that the Lal '934 disclosure regarding the uses of the SEQ ID NO:1-encoding polynucleotides for gene expression monitoring applications is **not** limited to the use of these polynucleotides as probes in microarrays. For one thing, the Lal '934 disclosure regarding the hybridization technique used in gene expression monitoring applications is broad (Lal '934 application at, e.g., page 4, line 22 to page 5, line 9; and page 6, line 35 to page 7, line 23).

In addition, the Lal '934 specification repeatedly teaches that the polynucleotides described therein (including the SEQ ID NO:2 polynucleotide) may desirably be used as probes in any of a number of long established "standard" non-microarray techniques, such as Northern analysis, for conducting gene expression monitoring studies. See, e.g.:

(a) Lal '934 application at page 30, lines 29-33 ("In general, host cells that contain the nucleic acid sequence encoding CYTPV and that express CYTPV may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.");

(b) Lal '934 application at page 49, lines 13-16 ("The polynucleotide sequences encoding CYTPV may be used in . . . northern analysis, dot blot, or other membrane-based technologies . . . Such qualitative or quantitative methods are well known in the art.");

(c) Lal '934 application at page 49, lines 27-33 ("In order to provide a basis for the diagnosis of a disorder associated with expression of CYTPV, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding CYTPV, under conditions suitable for hybridization or amplification.

Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used.") (emphasis supplied); and

(d) Lal '934 application at page 59, lines 10-13 ("Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)").

The "Sambrook" reference cited in item (d) immediately above is a reference that was well known to persons skilled in the art in July 2000. A copy of pages from that reference manual, which was published in 1989, is annexed to this Declaration at Tab H. The attached pages from the Sambrook manual provide an overview of Northern analysis and other membrane-based technologies for conducting gene expression monitoring studies that were known and used by persons skilled in the art for many years prior to the July 14, 2000 filing date of the Lal '934 application.

Thus, a person skilled in the art on July 14, 2000, who read the Lal '934 specification, would have routinely and readily appreciated that the SEQ ID NO:1-encoding polynucleotides disclosed therein would be useful as probes to conduct gene expression monitoring analyses using Northern analysis or any of the other traditional membrane-based gene expression monitoring techniques that were known and in common use many years prior to the filing of the Lal '934 application. For example, a person skilled in the art in July 2000 would have routinely and readily appreciated that the SEQ ID NO:1-encoding polynucleotides would be useful tools in conducting gene expression analyses, using the Northern analysis technique, in furtherance of (a) the development of drugs for the treatment of cell proliferative, developmental, autoimmune/inflammatory, liver, and metabolic disorders, and (b) analyses of the efficacy and toxicity of such drugs.

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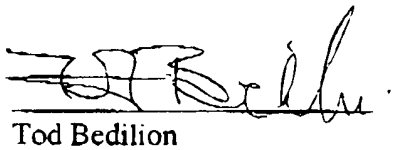
17. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.



Tod Bedilion

Signed at Redwood City, California
this 18th day of August, 2003.